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14. ABSTRACT
Purpose and scope: A large genetic association study is being conducted, to examine relationships of prostate cancer risk with polymorphic variation in a series of selected candidate genes that are involved in pathways determining the synthesis of IGF-I and IGF-binding proteins, as well as biological response to IGF-I. The study is being performed within a large Swedish case-control study ("CAPS"). Progress report: We have distributed the selected DNA, selected haplotype tagging SNPs to be analyzed for all candidate genes, and have completed about three quarters thirds of all genotyping assays for the prostate cancer cases and control subjects. We have completed analysis for the IGF1, IGFBP3, IGFBP1 and GHR genes using the linked database, containing data on tumor grade, stage and serum PSA levels, for all prostate cancer cases. Associations with genetic variation in IGF1 and GHR were noted. Plasma assays of IGF-I and IGFBP-3 are also nearly completed. Conclusions: We have globally made very important progress on this project, which will lead to a total of at least five scientific publications with the laboratory measurements produced thus far. However, due to administrative errors in the transfer of funds, we have been able to complete only about half of the genotyping assays that were originally planned. Proper receipt of the funding, and extension of the study period by one year, should allow us to complete the study fully according to the initial work plan.

15. SUBJECT TERMS
Insulin-like growth factor-I (IGF-I), Genetic Polymorphisms, Epidemiology, Prostate Cancer Risk

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Introduction

Evidence is rapidly accumulating that insulin-like growth factor-I (IGF-I) can enhance the development of tumors in different organs. Studies *in vitro* have shown that IGF-I inhibits apoptosis and stimulates cell proliferation in a wide variety of cell types. Furthermore, tumor development can be strongly enhanced in animals or organs that have been genetically or otherwise manipulated to either over express IGF-I or the IGF-I receptor, whereas animals made deficient in IGF-I are protected. Experiments with IGF-I$^{-/-}$ null mice have shown that normal IGF-I levels are required for prostate gland development, and transgenic mice expressing human *IGF1* in basal epithelial cells of the prostate have a high spontaneous incidence of prostatic tumors. In men, several prospective cohort studies and case-control studies have shown an increased prostate cancer risk among men who have elevated plasma IGF-I levels – expressed either as absolute concentrations, or relative to levels of IGFBP-3, IGF's major plasmatic binding protein.

Most of IGF-I and IGF-binding proteins in the circulation originates from the liver, but all peptides are also formed in other organs, including the prostate, where they exert paracrine and autocrine effects. Circulating IGF-I, as an endocrine factor, can diffuse towards its target tissues. In addition, IGF-I synthesis by the liver and many other organs is very much controlled by the same endocrine and nutritional factors. The major endocrine stimulus to IGF-I synthesis, in liver and many other tissues, is provided by growth hormone (GH). Thus, elevated IGF-I in blood most likely reflects an elevated pituitary GH secretion, and most likely indicates also elevated levels in other tissues where GH also provides the principal stimulus to IGF-I synthesis.

Given the increasing evidence that elevated IGF-I may enhance cancer development, it is important to understand what factors can lead to elevated IGF-I in the circulation and tissues. Besides nutritional status (Kaaks & Lukanova, 2001), heritability studies have shown that, at least in western, well-nourished populations, a large part (40-60 %) of variation in IGF-I is (co-) determined by genetic factors (Hong et al., 1996; Harrela et al., 1996; Verhaeghe et al., 1996). So far, however, no studies have been published, reporting a comprehensive search for polymorphisms in a full panel of genes involved in regulating IGF-I synthesis, and correlating such a panel with inter-subject variations in IGF-I and IGFBP-3 levels.

Besides the genes for IGF-I (*IGF1*) and IGFBP-3 (*IGFBP3*), major candidate genes to be examined are those involved in the pituitary release or biological action of growth hormone — the primary physiological stimulus for the synthesis of both IGF-I and IGFBP-3. This latter includes the genes for somatostatin (*SST*) and its receptors (*SSTR1-5*), pituitary-specific transcription factor (or POU-domain class 1 transcription factor 1 (*POU1F1*); growth hormone (*GH1*) and its receptor (*GHR*), growth hormone releasing hormone (*GHRH*), and the GHRH receptor (*GHRHR*). Ghrelin (*GHRL*), a recently identified new peptide hormone produced by endocrine cells in the stomach, also stimulates growth hormone secretion. It is the first identified natural ligand for a previously cloned growth hormone secretagogue receptor (*GHSR*) which is present in the pituitary gland and the hypothalamic region of the brain. In the circulation, IGF-I and a large percentage of IGFBP-3 are bound to a third peptide, referred to as Acid Labile Subunit (*IGFALS*) which has a key role in stabilizing the circulating pool of these peptides, and in regulating IGF-I release towards tissues. For each of these genes, polymorphisms that change gene expression or protein function can be expected to result in a relative increase or decrease in circulating IGF-I or IGFBP-3 levels.

The specific aims of our project are the following:

- to examine associations of prostate cancer risk with polymorphic variants (single nucleotide polymorphisms [SNPs] or their haplotypes) of selected candidate genes that may determine the synthesis and circulating levels of IGF-I, or and biological response to IGF-I;
- to confirm that elevated IGF-I levels, as absolute concentrations or expressed relative to concentrations of IFBP-3, are associated with an increased risk of prostate cancer; and
- examine whether associations of prostate cancer risk with polymorphic gene variants can be explained, at least in part, by associations of the same gene variants with circulating IGF-I or IGFBP-3 levels.

Table 1. Candidate genes for studies of association with plasma IGF-I, IGFBP-3, and prostate cancer risk.

Gene	**Name and Function of gene product**
IGF-I	Insulin-like growth factor-I
GH1	Growth hormone: Main stimulus for synthesis of IGF-I and IGFBP-3
GHR	Growth hormone receptor: mediates GH effects
GHRH	Growth hormone releasing hormone: stimulates pituitary GH release
GHRHR	Growth hormone releasing hormone receptor; Mediates GHRH effects
SST	Somatostatin; inhibits pituitary GH release
SSTR1 – SSTR5	Somatostatin receptors, types 1 - 5; mediate SST effects on pituitary GH release
POU1F1	pituitary-specific transcription factor; crucial for pituitary GH synthesis
IGF1R	IGF-I receptor
GHRL	Ghrelin
GHSR	Growth hormone secretagogue receptor
IGFALS	IGF binding protein, acid labile subunit
IGFBP1 - 6	IGF-binding proteins 1 to 6

For year 1, our tasks, as in the "Statement of Work" of our original grant application, were the following:

Task 1: Completion of the recruitment of prostate cancer cases and control subjects into the Swedish "CAPS" (CAncer of the Prostate Sweden) project, using suitable matching and selection criteria for the controls subjects; Storage of blood samples (plasma and buffy coats) in the Medical Biobank at Umeå University;

This objective was entirely achieved, and actually even exceeded: A total of 2831 prostate cancer cases (57 percent of which were localized tumors, and 43 percent locally advanced tumors) and 1784 control subjects were recruited into the CAPS project, and from these subjects questionnaire data and blood samples were collected as planned. Blood samples were fractionated into plasma and buffy coats, and stored in the Umeå Medical Biobank. The increase in numbers of prostate cancer cases and control subjects was motivated by the fact that the speed of subject recruitment could be accelerated (thus allowing a cost-effective extension of study size), plus the consideration that the sample size initially foreseen (1200 cases and 1200 control subjects) might have provided insufficient statistical power to examine associations of genetic polymorphisms with prostate cancer risk, by subsets of different tumor grade and stage (e.g., local *vs*. advanced tumors).

Task 2: Retrieval of plasma samples from the Medical Biobank, assembly of plasma samples into batches of case-control sets for immunoassay of IGF-I and IGFBP-3;

This task was completed in year 2 of the project, not in year 1, because of some changes in the agenda of the Hormones and cancer Laboratory where the assays of IGF-I and IGFBP-3 will be performed, and because we have to liberate freezer space at IARC where to store the plasma aliquots.

Task 3: DNA extraction from buffy coat samples of all prostate cancer cases and control subjects (total of 2400 subjects originally foreseen); and

This task was fully completed: DNA was extracted from the buffy coats of all 2831 prostate cancer cases, and 1784 controls.

Task 4: Preparation of microwell plates with DNA aliquots for genotyping of genetic polymorphisms, at IARC.

This task was also entirely completed: 500 ng. aliquots of DNA were distributed into microtiter plates and shipped to the IARC (shipped in May 2004).

For year 2, our tasks, as in the "Statement of Work" of our original grant application, were the following:

Task 5: Measurement of assays of IGF-I and IGFBP-3 in plasma of prostate cancer cases (n=1000) and controls (1200). Plasma samples have been shipped in year 2, from the central CAPS biobank in Umeå (Sweden) to the hormone assay laboratory at IARC (Lyon, France). These actual assays, however, are currently being performed at the hormone assay laboratory at IARC, and will be finished in June 2006.

Task 6: Genotyping of cases and controls for polymorphisms in genes related to the IGF system. An extensive search was made in the now publicly accessible "HapMap" database, which provides very detailed information about the presence of genetic variants and their linkage disequilibrium patterns, in genes throughout the genome. This search, combined with our own previous work for the identification of SNPs, has allowed us to make a more exhaustive screen of the genetic and haplotypic that exists in the candidate genes of the IGF1 pathway than initially envisaged. By following the 'haplotype tagging' SNP approach, discussed in the year one and two progress reports, allows greater efficiency in our genotyping strategy. One clear example is the GHR gene in which, following the protocol outlined by Stram et al. (2003), a total of 113 SNPs can be tested by only 19 htSNPs, with only minimal loss of information (due to the fact that SNPs are often in linkage disequilibrium, making measurement one SNP a measurement of others by proxy) (Stram et al., 2003) (**Table 2**).

Table 2. Haplotype-tagging (ht)SNPs' selected, and genotyping completed, in the CAPS study.

Genes	Genome size (kb)$^{\Psi}$	SNP's in gene region^{t}	htSNPs selected*	SNPs genotyped
IGF1	128	44	11	11
IGFBP1	24	10	6	6
IGFBP3	70	18	6	6
IGFALS	9	6	3	3
GHR	447	113	18	18

SST	46	18	4	2
SSTR1	18	6	4	3
SSTR2	16	8	6	6
SSTR3	40	29	6	4
SSTR4	8	3	5	5
SSTR5	19	9	5	4
GHRH	10	2	2	
GHRHR	37	13	8	
IGFBP2	66	12	8	
IGFBP5	29	9	6	
IGFBP4	18	7	7	
IGFBP6	26	6	5	

[Ψ]Genomic size including blocks of LD (defined by Gabriel et al., 2002 method) that may partially overlap with genomic sequence

[t]Number of confirmed polymorphic SNPs contained in the gene region (and in LD blocks that cover the gene) identified from the HapMap initiative and IARC SNP discovery work

*Selected on the basis of an R^2h>0.8 for SNPs inside haplotype blocks (defined by Gabriel et al., 2002 method) and R^2s>0.8 for SNPs falling in-between or just outside haplotype blocks if that distance is less than 10kB (Stram et al., 2003).

We have completed the genotyping of approximately three quarters of all htSNPs, totaling approximately 70 SNPs focusing first on the *IGF1*, *IGFBP1*, *IGFBP3*, *IGFALS*, *GHR*, *SST* and *SSTR1* to *SSTR5* genes. Tests of concordance with Hardy Weinberg equilibrium and quality control checks have also been completed for these 70 htSNPs.

Due to serious administrative errors in the transfer of funds from the DoD to IARC (see further comments at the end of this report) we have not yet been able to complete genotyping testing for the remaining genes (*IGFBP2*, *IGFBP4*, *IGFBP5*, *IGFBP6*, *GHRH*, *PouF1*, *GHRHR*, *GHRL*, *GHSR*).

Task 7: Linkage of study set to primary registry of four regions to obtain data on tumor grade, stage and serum PSA levels as well as date and type of cancer treatment. This task has been completed, and data (additional variables) have been added to the central CAPS database.

Tasks 8 and 9: Statistical analysis of associations between genetic polymorphisms, plasma levels of IGF-I, IGFBP-3 and risk of prostate cancer. We have completed statistical analyses on the relationship of prostate cancer risk with polymorphic variants in the *IGF1*, *IGFBP1*, *IGFBP3*, *IGFALS* and *GHR* genes. Notable associations were identified between genetic variation in *IGF1* and *GHR* and risk of prostate cancer risk. The statistical analyses for the genes *SST*, *SSTR1*, *SSTR2*, *SSTR3*, *SSTR4*, and *SSTR5* will be completed by summer 2006. By contrast, we have not yet started any statistical analyses on relationships between plasma IGF-I and IGFBP-3 levels, as these measurement assays are still in the process of being completed (will be complete in June 2006).

Task 10: Interpretation of data, writing of reports. Two papers have been prepared and submitted to peer-reviewed scientific journals:

- a paper describing the association of genetic variation in the IGF1 gene and prostate cancer risk has been provisionally accepted at the International Journal of Cancer; and
- a paper describing genetic variation in the gene GHR and prostate cancer risk is currently under peer-review at Cancer Epidemiology Biomarkers and Prevention.

Key research accomplishments, year 3

Accomplishments of year 3 include:

- Selection of haplotype tagging SNPs (htSNPs) for genes to be genotyped. Optimization of TAQMAN assays for the htSNPs
- Completion of genotyping in the case/control series at IARC in 4865 individuals for the genes *IGF1*, *IGFBP1*, *IGFBP3*, *IGFALS*, *GHR*, *SST*, *SSTR1* to *SSTR5*, and completion of assays for the first 75 percent of htSNPs to be typed (in May 2006, approximately 306,000 genotypes have been completed).
- Completion of a linked database containing data on tumour grade, stage and serum PSA levels has been assembled and distributed among the collaborating partners.
- The plasma samples have been shipped from the central CAPS biobank in Umeå (Sweden) to the hormone assay laboratory at IARC (Lyon, France) and assays are currently being performed at the hormone assay laboratory at IARC, with completion in June 2006.
- Statistical analysis has been completed for *IGF1*, *IGFBP3*, *IGFALS*, *GHR*, with statistically significant associations being found with haplotypes in *IGF1* and *GHR* and increased prostate cancer.

Reportable outcomes

Scientific Papers for peer reviewed scientific journals have been prepared for two genes where interesting associations have been found, IGF1 and GHR.
The associations seen for *IGF1* are of particular interest, as the haplotype in IGF1 which was associated with a approximately 50% increase in risk, has also been independently associated with increased circulating IGF1 levels:

- Al-Zahrani A, Sandhu MS, Luben RN, Thompson D, Baynes C, Pooley KA, et al. *IGF1* and *IGFBP3* tagging polymorphisms are associated with circulating levels of *IGF1*, *IGFBP3* and risk of breast cancer. Hum Mol Genet. 2005.
- Canzian F, McKay JD, Cleveland RJ, Dossus L, Biessy C, Rinaldi S, et al. Polymorphisms of genes coding for insulin-like growth factor 1 and its major binding proteins, circulating levels of IGF-I and IGFBP-3 and breast cancer risk: results from the EPIC study. Br J Cancer. 2006 Jan 30;94(2):299-307.)

One haplotype in the 3' end of end of the *GHR* gene was associated with risk in men with a more elderly age of onset. Interestingly we also found this haplotype associated with a decreased BMI, an outcome which would be consistent with a altered GHR function, strengthening the association.
Our analyses showed no associations of prostate cancer risk with polymorphic variations in *IGFALS*, *IGFBP1* and *IGFBP3*.

Some comments about the administrative errors

Although we have made substantial progress with this project, we have been hampered by some serious administrative problems in the transfer of funds from the US Dept of Defense (DoD) to IARC. This issue has been the subject of a long exchange of E-mails and some discussions by telephone, of which we provide a brief summary below:

- On July 9, 2003, we (letter signed by Ms W. Fevre Hlaholuk, Administrative Assistant at IARC) informed Mr. Archie Cardwell, contract specialist at the DoD, that inaccuracies had occurred with regard to the name of the contractor given on the cover page of the Award signed by Joseph S. Little, 24 April 2003. In fact, the contractor's name was listed as the "Centre de Recherche du Service de Santé, Institut de Médecine Tropicale du

SVC de S. Marseille (MTSS)" instead of rather than "International Agency for research on Cancer (or, in French, Centre International de Recherche sur le Cancer)"

- In this same letter, we informed Mr Cardwell of the fact that a cheque in the sum of $ 36,926.25 (No 5570-93,450,667) was received at "Centre de Recherche du Service de Sante in Marseille"**;**
- On July 30, 2004, an amended contract was sent to us by E-mail;
- On October 7, 2003, our budget & finance officer, Mr Raul Thomas, informed Mr Cardwell and Ms Melanie Harman) by E-mail that the French Army in Marseille had received two further cheques;
- On January 24, 2005, a new E-mail sent to Melanie Harman, with a cc. copy Mr Mishra, Grants Manager, explaining that we had not received any payments since March 2004 – the time at which we had received the final installment of $36,926.50 for Year 1. This E-mail message was forwarded from Mr Mishra to Mr Cardwell with a request to follow-up on this matter;
- On June 2nd, 2005, IARC sent a reminder to Mr Cardwell, who faxed us on June 27 a copy of the payment history, as documented at the DoD;
- June 27, 2005, IARC sent another E-mail to Mr Cardwell indicating that, as per documents faxed 27 June, 5 payments where still being sent to the French Army **(**total amount of 165,464.50$**):** it was 4 payments and not 5 at that time;
- On July 5th, 2005, IARC sent per E-mail to Mr Cardwell the E-mail address of a point of contact at the French Army : imtssa.finances@wanadoo.fr (Lieutenant YOU), to help Mr Mr. Cardwell take up contact with the French Army, and correct the errors made o=in money transfers;
- On July 27, 2005, an E-mail message from Lieutenant You, at the French Army informed Mr A. Cardwell the receipt in Marseille of a new check of $15,745 dated 15 July 2005 (corresponding to the fifth installment);
- On July 20, 2005, an E-mail message from Mr. Cardwell to Lieutenant YOU at the French Army stated that: ".... **There are 5 checks outstanding in the amount of $215,371** . I hereby request a check in that amount be disbursed to the following person : Mr P. Knoche, Budget & Finance Officer, WHO- IARC... " (Please note that, in our analysis, is not the exact amount to be transferred – The French Army should have received 5 cheques for a total amount of 181,209.50$ (3 x 49,906.50$ + 2 x 15,745$)
- August 31st, 2005, an E-mail and letter from Mr P. Knoche (Budget and Finance Officer at IARC) to J. Little & N. Mishra provided detailed information on the grant;
- November 23rd, 2005, a reminder was sent by E-mail from P. Knoche to J. Little (Cc. to N. Mishra); a copy was sent from J. Little to Mary Arriola for follow-up;
- February 14, 2006, a new reminder (E-mail) was by Mr Knoche to J. Little;
- February 15, 2006, an E-mail message from J. Little to Ms Mary Arriola, and a reply from Ms Arriola, indicated that the last payment was sent Jan. 26, 2006 to the French Army in Marseille (Check 93516943);
- February 21st, 2006, an E-mail from P. Knoche to J. Little & M. Arriola explained that we had no relationship with the French Army in Marseille and that we never received the missing cheques;
- February 2006, an E-mail message from Mr P. Knoche to J. Little & M. Arriola confirmed the receipt of one cheque Check (nr. 93516943), in the amount of $15,745, sent directly from the French Army in Marseille ?;

In spite of the extensive E-mail communications about this issue between IARC and the DoD, IARC still has not received the majority of the funds that we entitled to receive, according to our

contract. The **total amount outstanding on this grant as at 13 March 2006 equals $181,209.50 (3 payments year 2 and 2 payments year 3).**

Until the middle of year three of this project, our institute (International Agency for Research on Cancer; IARC) continued providing financial advances to enable us to proceed with the study, on the expectation of eventually receiving the funds that are due from DoD. In February 2006, however, the administration of IARC decided to stop providing further advances, and we have been forced to suspend our work. This is the key reason why we have not been able to complete the genotyping for the candidate genes of *IGFBP2*, *IGFBP4*, *IGFBP5*, *IGFBP6*, *GHRH*, *PouF1*, *GHRHR*, *GHRL*, *GHSR*).

Tasks still to be completed; proposal to extend the study period by one year
The following additional publications are planned, with the laboratory assays completed so far:

- Prostate cancer risk in relation to polymorphic variants in the *IGFBP1*, *IGFBP3* and *IGFALS* genes;
- Prostate cancer risk in relation to polymorphic variants in *SST*, *SSTR1*, *SSTR2*, *SSTR3*, *SSTR4*, *SSTR5*;
- Polymorphic gene variants in relation to plasma levels of IGF-I and IGFBP-3; and
- Prostate cancer risk in relation to plasma concentrations of IGF-I and IGFBP-3.

In addition, we still plan to complete the genotyping for the genes *IGFBP2*, *IGFBP4*, *IGFBP5*, *IGFBP6*, *GHRH*, *PouF1*, *GHRHR*, *GHRL*, *GHSR*. For this purpose, we request an extension of the study period by one year. However, given the elevated reagent cost for genotyping, we note that the completion of this last part of the study will depend be entirely contingent on the receipt of funds from the DoD.

Proposed change in PI
The current Principal Investigator of this project, Dr Kaaks, has taken up new functions as Head of the Division of Cancer Epidemiology at the German National Cancer Center (Heidelberg, Germany). In view of his pending move to Heidelberg in August 2006, and assuming that DoD agrees with an extension of the study period by one year, we request that the PI-ship of this project be transferred to Dr James McKay, one of the other investigators at IARC, that has contributed most to the progress of this project during the last year.

Conclusions

We have put into place the biological samples and database needed to complete the CAPS studies investigation of the genes of the IGF1 pathway. For all candidate genes we have performed “tagging” analyses, to determine minimum sets of SNPs to be genotyped, covering all common haplotypic variations in these genes. For the genes *IGF1*, *IGFBP1*, *IGFBP3*, *IGFALS*, *GHR*, *SST*, *SSTR1*, *SSTR2*, *SSTR3*, *SSTR4*, *SSTR5* all genotyping assays have been designed, optimized and completed. Assays of plasma IGF-I and IGFBP-3 are also nearly completed for all prostate cancer cases and controls. Two publications have been submitted to scientific journals, and three further publications are planned with the laboratory assays that have been completed so far.
For the remaining genes (*IGFBP2*, *IGFBP4*, *IGFBP5*, *IGFBP6*, *GHRH*, *PouF1*, *GHRHR*, *GHRL*, *GHSR*), analyses for SNP-tagging have also been nearly completed, and assays for these tag-SNPs are being designed. However, the completion of the latter genotyping assays will entirely depend on the receipt of the complete funds for this project.

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Appendices

None